

### REMARKS

Claims 1, 2, 5-14, 35, 36, and 39-48 are currently pending and have been rejected by the Examiner under 35 U.S.C. § 103(a) over various cited publications. Based on the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw these rejections. Applicants have amended claims 1 and 35 to delete certain language relating to the method of producing the nanofibers, which was added in the last amendment. Given the Examiner's remarks that those limitations are process limitations in a product by process claim, Applicants believe the deletion of those limitations will have no affect on the claims, do not raise new issues and do not introduce new matter. Accordingly, Applicants respectfully request that these amendments be entered.

In the event that the Examiner is not ready to issue a Notice of Allowance after reviewing this document, the Examiner is respectfully requested to contact the undersigned to schedule an interview with Applicants or Applicants' representative.

**I. *Rejections of claims 1, 2, 5-7, 9-11, 13, 14, 35, 36, 39-41, 44, 45, 47, and 48 under 35 U.S.C. §103(a) over WO 01/89572 A1 to Seitz et al. ("Seitz") in view of WO 01/00149 A1 to Wheatley et al. ("Wheatley")***

**i. *Seitz***

The Examiner alleges that Seitz "teaches a biocompatible system for generating nitric oxide from sodium nitrite, ascorbic acid, and maleic acid upon treatment with water" and that the "reactants can be sequestered in separate gels that are then admixed or applied as layers to a substrate such as skin."

Seitz discloses a method for generating nitric oxide that "comprises combining a nitrite salt, a reductant and a mild acid" (see page 4, lines 2-4) and "involves more than one gel" (see page 4, lines 10-11). Particularly, "the first aqueous gel comprise a nitrite salt and a second gel comprise an acid with sufficient acidity to degrade the nitrite salt to nitric oxide." See page 4, lines 11-12). The "first and second gels may be combined in layers with the nitrite-containing gel preferably in contact with skin. Prior to application these gels could be separated by an impermeable plastic or metal foil in desired." See page 4, lines 20-22. These descriptions clearly illustrate that Seitz's invention entails mixing a nitrite salt and an acid (which are originally contained in different gels one of which may also contain a reductant), once these two

gels are in contact with each other. In other words, the mixture of the nitrite and the acid is still contained in at least one of the two gels, mostly likely in the gel that is applied directly onto the skin. The nitrite and the acid *are not released* from their respective gels, let alone the gels are not in the presence of a release agent. Seitz also points out that a “mixture of powered sodium nitrite, ascorbic acid, (or other reductant) and maleic acid (or another organic acid of adequate strength) immediately generates nitric oxide on treatment with water.” See page 4, lines 26-28. Under this statement, the water does not cause the nitrite and acid to be released from the respective gels in which they are contained. Rather, “treatment with water” causes the already mixed nitrite, reductant, and acid with adequate strength to “immediately [generate] nitric oxide.”

Further, Seitz teaches using gels made of such gellification agents as hydroxymethyl cellulose, gelatin, agar, and silicic acid. As the Examiner admitted, Seitz does “not teach sequestration of the reactants by nanofibers.”

By contrast, claim 1 of this present application covers a *fibrous* assembly comprising a first *nanofiber* that sequesters a first reactive component, and a second *nanofiber* that sequesters a second reactive component; wherein at least the first or second nanofiber releases its reactive component when the nanofiber is *in the presence of a releasing agent*, and when *the at least first and second nanofibers release their reactive components*, the first and second reactive components react with each other to form a reaction product.

The features of this claimed fibrous assembly include at least: (1) its components include nanofibers each of which sequesters a reactive component, (2) the reactive component is released from the nanofiber when the nanofiber is in the presence of a releasing agent, and (3) the reactive components, after being released from the nanofibers which initially contain them, react to form a reaction product.

None of these features however is taught or suggested by Seitz. Rather, Seitz teaches using gels (as opposed to nanofibers); it teaches simply mixing the reactants (without having them all released from the gels containing them, let alone in the presence of a releasing agent); and it teaches that the mixture reacts to form nitric oxide (again without first releasing them all from the nanofibers containing them). It makes no suggestions of any of the features required by the fibrous assembly of claim 1. Thus, Applicants submit that Seitz does not render claim 1 obvious.

Claim 35, on the other hand, covers a fibrous assembly comprising a first nanofiber that sequesters a first reactive component, wherein the first nanofiber releases its reactive component when the nanofiber is in the presence of a releasing agent and the reactive component and the releasing agent react to form a reaction product.

Similar to claim 1, features of the fibrous assembly of claim 35 include at least: (1) it includes at least a nanofiber which sequesters a reactive component, (2) the nanofiber releases its reactive component when it is in the presence of a release agent, and (3) the released reactive component reacts with the releasing agent to form a reaction product.

Again, Seitz fails to teach or suggest any of these three features. Specifically, Seitz teaches using at least two gels that contain a nitrite and an acid, respectively (as compared to a nanofiber sequestering a reactive component). Notably, Seitz teaches mixing the nitrite and acid *in one of the gels* where they react to produce nitric oxide, so it does not provide a nanofiber as required by the present claim 35. The nitrite or acid is never released from the gel as required in claim 35. And there are neither released reactive components nor a release agent as required by claim 35. Again, in the fibrous assembly of claim 35, the reactive component is first released from the nanofiber in the presence of a releasing agent; and then the released reactive component reacts with the releasing agent that causes the reactive component to release from the nanofiber, to give rise to a product. In other words, Seitz also fails to teach or suggest any of the features of the fibrous assembly of claim 35 as described above. Therefore, Seitz alone also does not render claim 35 obvious under 35 U.S.C. 103(a).

However, the Applicants are aware that the rejection of claims 1 and 35 is based upon Seitz in combination with Wheatley. Accordingly, they also address Wheatley, first by itself and then, in combination with Seitz.

In the “Field of the Invention” section, Wheatly states that it relates to “delivery systems comprising polymeric fiber matrices, film coatings or braided/woven structures for the controlled release of bioactive compounds.” Specifically, it discloses “a system for delivery of bioactive compounds comprising a bioactive compound incorporated within or between a polymeric fiber matrix or linear assembly, film coating or braided/woven structure” (see page 3, lines 23-27); “a method for delivering a bioactive compound to a patient for controlled release of the bioactive compound in the patient” (see page 3, lines 28-30); and “methods for modulating the rate of

release of a bioactive compound from a delivery system for bioactive compounds comprising a bioactive compound incorporated within or between polymeric fibers” (see page 4, lines 7-11).

Admittedly, Wheatly teaches using polymeric fibers. However, based on the Wheatley’s description, it is obvious that Wheatly does **NOT** itself teach or disclose the claimed invention, which provides fibrous assemblies containing nanofibers sequestering reactive compounds that are released in the presence of a releasing agent and then react between themselves (as recited in current claim 1 of the present application) or with the releasing agent (as recited in claim 35 of the present application) to form a reaction product.

Thus, Wheatly does not even remotely teach or suggest any of the features of the fibrous assemblies of claims 1 and 35 as discussed above. In other words, Wheatly also does not render claims 1 and 35 obvious under 35 U.S.C. § 103(a). The Examiner appears to agree with this assessment, given that no rejection of the claims over Wheatley exists.

Consequently, the Examiner attempts to combine Seitz and Wheatley, arguing that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to utilize the polymer fiber substrates as taught by Wheatley in place of the gel substrates taught by Seitz, with a reasonable expectation of success.

Applicants respectfully disagree. Clearly, the two references are not combinable into an invention that would be operable to one of ordinary skill in the art. If Wheatley’s fibers are used, there is no evidence that the nitrite and acid set forth in the gels of Seitz would react as required by Seitz. The evidence in Seitz is clear. The nitrite and acid in Seitz are never released from the gels. If fibers were used, there is (1) no evidence that the nitrite and acid would react and (2) no evidence that the ingredients could or would be released. Furthermore, one of skill in the art, noting that the nitrite and acid react within one of the gels, would understand and reasonably conclude that the use of fibers would most likely not have the same affect as desired in Seitz. Thus, contrary to the Examiner’s position, there is clearly no reasonable expectation of success.

Moreover, Applicants are puzzled by the Examiner’s citation of Wheatly as a secondary reference in addition to Seitz to reject claims 1 and 35. In Applicants’ opinion, Wheatly clearly does not relate to the field to which the pending claims relate or the field of Seitz. Applicants do not see any common theme between these two publications, other than their use of polymers. As such, Applicants do not believe there would have been any motivation for a person skilled in the art to which the present application relate to combine Wheatly and Seitz.

Even if a person skilled in the art would combine Seitz and Wheatly (which does not seem to be the case), they still do not teach or suggest any of the features of the fibrous assemblies of claims 1 and 35 as discussed above. Therefore, Applicants respectfully submit claims 1 and 35 are not obvious over Seitz in view of Wheatly and request that the Examiner withdraw her rejection of these claims under 35 U.S.C. § 103(a) over Seitz in view of Wheatley.

As claims 2, 5-7, 9-11, 13-14 and claims 36, 39-41, 44-45, and 47-48 depend directly or indirectly from claim 1 or claim 35, respectively, both of which are now believed allowable, Applicants believe these dependent claims are also not obvious over Seitz in view of Wheatly.

***II. Rejections of claims 8 and 42 under 35 U.S.C. § 103(a) over Seitz in view of Wheatly and further in view of US 5,798,115 to Santerre et al. ("Santerre")***

Claims 8 and 42 depend from claims 1 and 35 respectively. Both claims recite the limitation that the reactive component is a urethane prepolymer, diamine or diol. The Examiner alleges that these two claims are obvious under 35 U.S.C. § 103(a) over Seitz in view of Wheatly and further in view of Santerre. Applicants respectfully disagree with this allegation.

Applicants have established above that Seitz and Wheatly, either alone or in combination, do not render claims 1 and 35 obvious. As claims 8 and 42 depend from claims 1 and 35, these two claims are also not obvious over Seitz in view of Wheatly.

The Examiner admits that neither Seitz nor Wheatley "teaches the urethane prepolymer and diamine or diol as required in claims 8 and 42." Santerre, on the other hand, teaches "bioresponsive pharmacologically active polymers and articles made therefrom" and discloses inventions relating "to polymeric compound and substrates such as implantable medical devices formed from or coated with the pharmacologically active polymeric materials." Admittedly, Santerre discloses "a diisocyanate (polyurethane prepolymer) reacting with a surface-activated tubing material by reaction of free isocyanates with active carboxylic acid, amine, or hydroxyl groups," and to the extent that that is all Santerre is cited for, the Applicants do not disagree. However, Applicants again argue that Seitz and Wheatley and Santerre are not combinable inasmuch as one or more of the patents, particularly the invention in Seitz, would not otherwise be operable upon such a combination. That is, any disclosure of a polyurethane prepolymer, amine, or hydroxyl compound does not render any of claims 1, 8, 35, and 42 obvious, since

Santerre does not teach or suggest that it is suitable for use with any of the features of Seitz as discussed above.

For the same reasons, even if a skilled person in the art would combine Seitz, Wheatly, and Santerre (which Applicants submit is not the case), the combination still would not render claims 1 and 35 obvious, let alone claims 8 and 42 which depend from claims 1 and 35 and recite an additional limitation.

**III. *Rejections of claims 9 and 43 under 35 U.S.C. § 103(a) over Seitz in view of Wheatley and further in view of Anand et al. "Ion-exchange resins: carrying drug delivery forward", DDT Vol. 6, No. 17, September 2001 ("Anand")***

Claims 9 and 43 depend from claims 1 and 35, respectively. They both recite the limitation that the reactive component is bound to an ion-exchange-resin bead. The Examiner rejected these two claims under 35 U.S.C. § 103(a) over Seitz in view of Wheatley and further in view of Anand.

Applicants have established above that Seitz and Wheatley, either alone or in combination, does not render claims 1 and 35 obvious. For the same reasons, claims 9 and 43, which depend from claims 1 and 35, are also not obvious over Seitz in view of Wheatley.

However, beyond that, Anand discloses using ion-exchange-resin beads as matrices as drug delivery systems. Anand also discloses that the ion-exchange resins might not be optimally applicable to the skin, external canals (e.g., nasal and ear), or other areas with limited quantities of eluting ions (see page 908, column 1, paragraph 1). Thus, Applicants do not even see a motivation for a person skilled in the art to combine these three references together in view of their different technical features and fields of use, and their common lack of teaching or suggestion of the features of the fibrous assemblies claimed in the present application.

For these reasons, Applicants also respectfully request that the Examiner withdraw the rejection of claims 9 and 43 under 35 U.S.C. § 103(a) over Seitz in view of Wheatley and further in view of Anand.

**IV. *Rejections of claims 12 and 46 under 35 U.S.C. § 103(a) over Seitz in view of Wheatley and further in view of US 5,650,447 to Keefer et al. ("Keefer")***

Claims 12 and 46 depend from claims 1 and 35, respectively. They both recite the limitation that the nanofiber dissolves or swells in the presence of the releasing agent. The

Examiner rejected these two claims under 35 U.S.C. § 103(a) over Seitz in view of Wheatley and further in view of Keefer. Applicants disagree.

As stated above, Applicants have established that Seitz and Wheatly, either alone or in combination, do not render claims 1 and 35 obvious. Thus, claims 12 and 46, which depend from claims 1 and 35, are also not obvious over Seitz in view of Wheatly.

The Examiner alleges that Keefer teaches “the administration of nitric oxide by release from a polymeric material in order to deliver ameliorating, prophylactic, or therapeutic drug dosing for restenosis and related disorders” and “explicitly [teaches] that the polymer of the polymer-bound compositions may dissolve in a physiological environment in order to desirably deliver the active agent.” Despite Keefer’s teaching of a polymer that can dissolve, this reference falls far from teaching or suggesting any of the features of the fibrous assemblies of claims 1 and 35. Thus, it does not render obvious claims 1 and 35, or claims 12 and 46 which depend from claims 1 and 35.

The Examiner further alleges that “[both] Seitz and Keefer are directed to devices for the prophylactic or therapeutic administration of nitric oxide. Thus, it would have been *prima facie* obvious to one of ordinary skills in the art ... to employ the polymer dissolution features as taught by Keefer et al. in the devices of Seitz, with a reasonable expectation of success. One would have been motivated to do so in order to impart the biodegradable feature as taught by Keefer et al., thereby eliminating the need for fiber removal post delivery of the bioactive agent.”

Again, Applicants respectfully disagree with the Examiner’s allegation. Again, Applicants note that Seitz *requires* the use of gel for the reactants. There is simply no evidence as to what the affect would be to replace this gel and then dissolve its replacement. Clearly, Seitz is just no compatible with the Wheatley reference, not Keefer in combination with Seitz and Wheatley. Thus, there is no possible combination of Seitz and Wheatley and Keefer that would render claims 12 and 46 obvious.

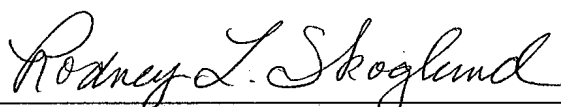
Thus, Applicants submit that claims 12 and 46 are not obvious under 35 U.S.C. § 103(a) over Seitz in view of Wheatley and further in view of Keefer, and respectfully request the Examiner withdraw this rejection.

In light of the foregoing amendments and arguments, Applicants believe that they have successfully overcome the Examiner’s various rejections of the pending claims, as currently

amended. Accordingly, the Examiner is respectfully requested to withdraw the rejections, a formal Notice of Allowance for claims 1, 2, 5-14, 35, 36, and 39-48 being earnestly solicited.

No fee is believed due with the filing of this document, except for the extension fees provided with the accompanying petition. Nonetheless, in the event that a fee required for the filing of this document is missing or insufficient, the undersigned attorney hereby authorizes the Commissioner to charge payment of any fees associated with this communication or to credit any overpayment to Deposit Account No. 18-0987.

Respectfully submitted,

A handwritten signature in cursive script, reading "Rodney L. Skoglund". The signature is written in dark ink and is positioned above a horizontal line.

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